

chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or  $\text{CO}_2\text{R}^4$  where  $\text{R}^4$  is hydrogen or  $\text{C}_1\text{-C}_9$  straight or branched chain alkyl or alkenyl;   
or a pharmaceutically acceptable salt, ester, or solvate thereof.

*a5* 25. (Amended) The method of claim 14, wherein the carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring is selected from the group consisting of compounds 146-165, 186-202, 366-385, 406-422, [1-442,] compound L, and compound M, or a pharmaceutically acceptable salt or solvate thereof.

*a6* Please add the following new claim:

*Rule 1.126* ~~71~~ <sup>72</sup> The compound of claim 1, wherein the compound is selected from the group consisting of compounds 146-165, 186-202, 366-385, 406-422, compound L, and compound M, or a pharmaceutically acceptable salt or solvate thereof. *a7*

**REMARKS**

Claims 1-11, 14-25, and 72 are pending in the present application. The claims have been amended in the expectation that the amendments will place this application in condition for allowance. The majority of the amendments have been made to remove non-elected subject matter from the scope of the claims. Basis for the amendments may be found within the specification as follows:

Claim 1 "C, CH" (the compounds disclosed on page 8, line 1; page 17, line 1; and claim 3 of the original specification as filed). The amendments do not introduce new matter within the meaning of 35 U.S.C. § 132. Accordingly, entry of the amendments is respectfully

requested.

**1. Restriction/Election Requirement**

The Official actions states that the Restriction/Election requirement has been finalized for the following reasons:

Applicant's election with traverse of group I, claim 5 wherein n=1 five membered ring compounds, with (2S)-1-(3, 3-dimethyl-1, 2-dioxopropyl)-2-(3-thiazolidine)carboxylic acid as the elected species in Paper No. 12, dated October 8, 1999 is acknowledged. The traversal is on the grounds that there is no serious burden to search the Markush claims. This is not found persuasive because the reason for restriction is that the claims are drawn to independent and patentably distinct compounds which differ in elements, bonding arrangements and chemical properties to such an extend that a reference anticipates a compound would not render another compound in the same obvious. It is noted that the compounds being proviso out at the end of claim 1 and a structural delineation of these compounds attached to paper No. 10 dated Oct. 21, 1999 have structural diversified rings for independent and distinct uses e.g.: CA 120:323484, L4-6 membered ring compound as angiotensin II receptor antagonists; CA 105:133909, L1-six membered ring as antihypertensives; CA 122:314456, L3-thiaxozolidines as intermediates for making anti-inflammatory; CA 97:88995, L3-thiasozolidines as metalloproteinase inhibitors; CA 76:140885, L3-oxazolidines as antidepressants; CA 76:99688 L1-thiaxozolidines as intermediates for making cephalosporin; CA 93:168254, L4-thiaxalidines as antibacterial. It is evidenced that not only the different size rings are structural material for distinct utility, but also the A moieties being drawn to the different structure are independent material for identifiable diversified utilities. In the event that applicant's traversal is also on the ground that the species are not patentably distinct, applicant did not submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the

case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention. If such identification or admission were made, then there could have been no patentability of all the inventions over Yoshida et al. US 4,510,154 (see col. 15-16 compounds 50, 52 anticipated the claims when the heterocyclic ring is substituted, A is L4, R2 is carboxylic isostere triazole, i.e. CA 115:92147).

According to MPEP 803.02 restriction for Markush claims, broadly, unity of invention exists where compounds included with a Markush group (i) share a common utility and (ii) share a substantial structural feature disclosed as being essential to that utility. From the above evidenced provided by applicants proviso out from the claims, no common core essential to the claimed utility can be found for the Markush claims.

Based on the election of group I and the species of (2S)-1- (3, 3-dimethyl-1, 2-dioxopropyl) -2- (3-thiazolidine)carboxylic acid, the subject matter being examined is limited to n=1, A=L1 compounds. Claims 1-11 reading on the elected compounds are examined together with claims 14-25 limited to treating Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Claims 12-13, 26-71 and the remaining compounds or methods of claims 1-11, 14-25 are withdrawn from consideration per 37 CFR 1.142(b).

The requirement is still deemed proper and is therefore made final.

Applicants have amended the claims so that they are now directed solely to elected subject matter. Non-elected subject matter has been removed from the claims without any prejudice or disclaimer to the removed subject matter.

## 2. Submitted References

The Official Action states that submitted references have been reviewed as follows:

An enormous number of prior art references have been

submitted without description of relevancy. These references as cited on the 1449 have been given a **cursory** review commensurate to the manner they are submitted.

Applicants would like to point out to the Examiner that a Letter to the Examiner was filed on December 30, 1999 describing the particular relevancy of the cited references, a copy of which is included for the Examiner's convenience.

**3. Rejection of Claims 1-11 under 35 U.S.C. § 112, 2d paragraph**

The Official action states that claims 1-11 are rejected under 35 U.S.C. § 112, second paragraph for the following reasons:

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Confusion that claims 1-11 failed to correspond in scope with that which applicant(s) regard as the invention can be found in the inconsistency among the claims. Please note that I) in claim 1, the R2 moiety is a carboxylic acid or a carboxylic acid isostere. While ester of a carboxylic acid is considered an "isostere", an hydroxy/hydroxyalkyl group has not been recognized in the art as such an isostere.

ii) in claim 2, the R2 moiety was limited to cyclic structures containing CH<sub>2</sub>, O, S, or N, while those disclosed in p. 8 (or claim 3) do not contain such structure (please note that none of the structures in p. 8 has a CH<sub>2</sub> node nor does the descriptive scope of R3 substituents include oxo;

Applicants respectfully traverse this rejection. Regarding the §112, second paragraph rejection, caselaw has defined two requirements under the statute: (1) whether the applicant has stated the invention as something elsewhere in the application which would not fall under the scope of the claims; and (2) whether

the claims would be communicated with a reasonable degree of particularity and distinctness to a person skilled in the art in light of the content of the disclosure and the teachings of the prior art. MPEP §2171, §2173, and §2173.02.

Regarding point I of the rejection, Applicants would like to point out to the Examiner that an ester is not considered a carboxylic acid isostere according to the scope of the present invention. It is well recognized that "[A] patentee is free to be his own lexicographer. See Markman v. Westview Instruments, Inc., 52 F.3d 967, 980, 34 USPQ2d 1321, 1330 (Fed. Cir. 1995) (in banc), aff'd, 116 S. Ct. 1384, 38 USPQ2d 1461 (1996). In the present application, Applicants have provided a definition for carboxylic acid isosteres on page 16, line 17 to page 18, line 20. Nowhere do Applicants define an ester as a carboxylic acid isostere. Accordingly, esters are not considered carboxylic acid isosteres as defined by the present invention.

Conversely, Applicants specifically define both the hydroxy and hydroxyalkyl (assuming that the Examiner is referring to -OR<sup>3</sup>) groups as carboxylic acid isosteres on page 16, line 25. Accordingly, both of these groups are recognized in the present invention as carboxylic acid isosteres.

Regarding point II of the rejection, Applicants thank the Examiner for her suggestion regarding the claims. Applicants have

amended the R<sub>2</sub> moiety of claim 2 to include cyclic structures containing C, CH, and CH<sub>2</sub>. These substituents can be found in the structures disclosed in page 8 (and in claim 3).

Applicants would further like to point out to the Examiner that the structures found in claim 3 only represent possible carboxylic acid isosteres of R<sub>2</sub>. Any oxo found in these structures is a necessary element of the particular embodied carboxylic acid isostere, and accordingly is a part of R<sub>2</sub> and not R<sub>3</sub>. As defined on page 16 (lines 28-33), chemically stable oxidative states of C are included in the definition of isostere. (See also claim 2). Therefore, the substituents in claim 3 are not inconsistent with those of claims 1-2, and are directly derived therefrom.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection to claims 1-11.

**4. Rejection of Claims 1-4 under 35 U.S.C. § 102(b)**

The Official action states that claims 1-4 are rejected under 35 U.S.C. § 102(b) as being anticipated by Henery-Logan, Andrew, or Dunkerton.

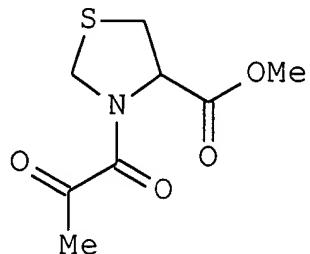
As the basis of this rejection, the Official action states:

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Henery-Logan CA 79:31977, or Andrew CA 128:114889, or Dunkerton CA 94:84059, see structural delineation of compounds attached.

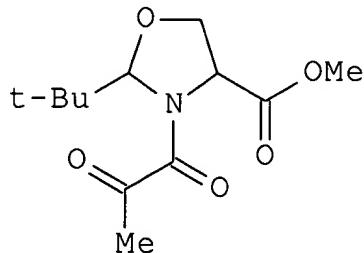
Applicants respectfully traverse this rejection. The test for anticipation is whether each and every element as set forth is

found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

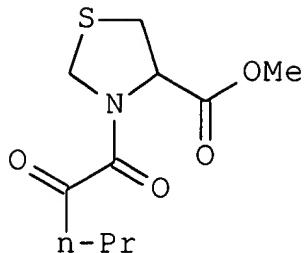
The Henery-Logan reference discloses the following compound:



The Andrews reference discloses the following compound:



The Dunkerton reference discloses the following compound:



Each of these references disclose a species having a methyl ester attached at the 2-position of the central heterocyclic ring. These compounds have previously been removed by proviso.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection to claims 1-4.

**5. Rejection of Claims 1-5 under 35 U.S.C. § 103(a)**

The Official Action states that claims 1-5 are rejected under 35 U.S.C. § 103(a) as being obvious over Henery-Logan or Andrew or Dunkerton.

As the basis of this rejection, the Official Action states:

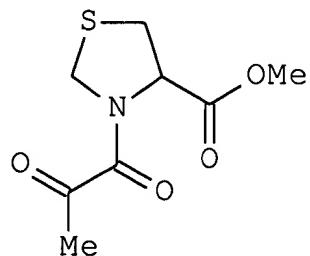
Henery-Logan CA 79:31977, or Andrew CA 128:114889, or Dunkerton CA 94:84059 disclosed compounds anticipated the base claim. The difference between the claims i.e. the elected species and the prior art is in the addition of additional straight or branched alkyl chain. The variation of chain length is normally not patentable in absence of unexpected results because to those skilled in chemical art one homologue is not such an advance over adjacent member of series as requires invention unless beneficial properties realized in new homologue lie clearly outside of expectation. In re Wood 199 USPQ 137; In re lohr 137 USPQ 548; In re hoke 195 USPQ 148; In re Fauque 121 USPQ 425.

Applicants respectfully traverse this rejection. The references of record do not teach or suggest Applicants' inventive

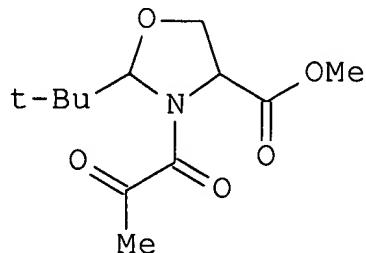
subject matter as a whole as recited in the claims. It is not even apparent what would lead the ordinary skilled artisan to modify the cited references to derive the subject matter claimed by Applicants.

The U.S. Supreme Court in *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (1966) held that non-obviousness was determined under § 103 by (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and, (4) inquiring as to any objective evidence of nonobviousness.

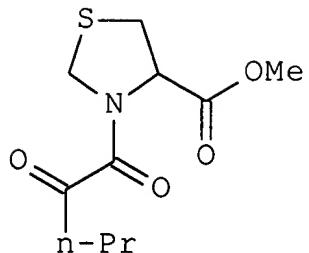
The Henery-Logan reference teaches the following compound:



The Andrews reference teaches the following compound:



The Dunkerton reference teaches the following compound:



The Henery-Logan, Dunkerton, and Andrews references each teach that the disclosed compounds are useful as intermediates. No other use for these compounds is disclosed. One skilled in the art would not be led by the cited references to make the claimed compounds.

None of the cited references disclose the ability of the embodied compounds to grow nerves. This is an unexpected property of the present inventive compounds. Under In re Albrecht, 198 U.S.P.Q. 208 (C.C.P.A. 1978), an unexpected property possessed by a compound is evidence of its unobviousness.

The Examiner cites four cases in support of her position. However, none of these cases are directly on point in the present application.

In Ex parte Fauque, 121 U.S.P.Q. 425 (B.P.A.I. 1954), the difference between the prior art compound and the claimed compound was the substitution of two methyl groups rather than hydrogen on each of two different furan rings. Both the prior art compound and the claimed compound were useful for forming resinous polymers.

In In re Lohr and Spurlin, 137 U.S.P.Q. 548 (C.C.P.A. 1963), the difference between the claimed compounds and the prior art

compounds was the presence of two methyl groups at the 2 and 6 positions of a heterocyclic nucleus. Both the claimed compounds and the prior art compounds were useful as a pesticide.

In In re Hoke, 195 U.S.P.Q. 148 (C.C.P.A. 1977), the difference between the claimed compounds and the prior art compounds was the presence of methyl radicals instead of hydrogens on the ring structure. Both the claimed compounds and the prior art compounds were useful as flocculants.

In In re Wood, Whittaker, Stirling, and Ohta, 199 U.S.P.Q. 137 (C.C.P.A. 1978), the difference between the claimed compounds and the prior art compounds was the presence of two methyl groups at the 7,7 position of the heterocyclic ring. Both the claimed compounds and the prior art compounds possessed antimicrobial activity.

Each of the cited cases involve a prior art compound having the same utility as the claimed compound. However, the present situation involves claimed compounds which possess a unique activity not suggested by any of the cited references. The claimed compounds are clearly disclosed as being useful in the treatment and growth of damaged nerves. None of the cited references even suggest that the embodied compounds possess this utility. See In re Lunsford, 148 U.S.P.Q. 721 (C.C.P.A 1966) in which non-obviousness was established based on different utilities between

the claimed compound and the alleged prior art homolog.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection.

It is readily apparent that there is no disclosure of facts in the prior art which support a legal conclusion that the claimed invention was obvious at the time it was made. It is a well settled principle that prior publications are references only for what they clearly disclose or suggest and that it is not proper use of a publication as a reference to modify its structure to one which the reference does not suggest.

It is readily apparent from the references relied upon that the technology disclosed in the present application is totally unrelated to that which is disclosed by these references. The cited references, taken as a whole, do not disclose each and every element required by the claimed compounds.

The provisions of Section 103 must be followed realistically to develop the factual background against which the Section 103 determination must be made. All of the facts must be considered and it is not realistic within the framework of Section 103 to pick and choose from any one reference only so much as will support a given position to the exclusion of other parts necessary for the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. Accordingly, withdrawal of the

rejection and an allowance of claims 1-5 is respectfully requested.

**6. Rejection of Claims 1-11 and 14-25 for  
Obviousness-Type Double Patenting**

The Official Action states that claims 1-11 and 14-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,801,187.

As the basis of this rejection, the Official action states:

Claims 1-11 and 14-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,801,187. Although the conflicting claims are not identical, they are not patentably distinct from each other because to the extend that carboxylic isosteres included carboxylic ester, over lapping subject matter are claimed. To the extend that the carboxylic acid isosteres are drawn to those art recognized *prima facie* obvious variations of the isosteres, claims 1-11, 14-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,801,187 in view of EP 400,974. The difference between the compounds of the instant claims and those of Li et al. '187 is the replacement of one carboxylic acid isostere with another conventional known isostere (see EP400974, p.2-3 isosteres of carboxylic acids). The term "isostere" is the equivalency of carboxylic acid moiety. Employing one equivalence in place of another is the conventional skill of isosterism. There is nothing unobvious in employing the well documented skill of the art with the exact expectation of the skill of isosterism.

Applicants respectfully traverse this rejection. The '187 patent is directed solely to compounds having an ester attached at the 2-position of the central heterocyclic ring. The claimed compounds have a carboxylic acid or carboxylic acid isostere

attached at the same position.

Applicants would like to point out to the Examiner that, as stated above, an ester is not considered a carboxylic acid isostere and is not within the scope of the present invention. Accordingly, the present claims are patentably distinct from those of the '187 patent based on a lack of overlapping subject matter.

Additionally, the Examiner cites pages 2-3 of EP 400,974 as showing various isosteres of carboxylic acid. However, there is no suggestion in the cited reference that contradicts the definition found in the present application. However, a carboxylic acid derivative is a compound which was derived from a carboxylic acid, or from which a carboxylic acid was the starting material. Accordingly, the EP 400,974 reference offers no teaching that makes the present invention obvious over that art. There is no teaching to combine the two cited references to overcome the definition found in the present application.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-11 and 14-25.

#### CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of remaining

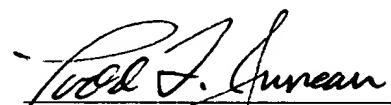
claims 1-11, 14-25, and 72 and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if he has any questions or comments.

Respectfully submitted,  
**NATH & ASSOCIATES PLLC**

Date: May 8, 2000

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